NTP
National Toxicology Program

Toxicology and Carcinogenesis Studies of Ginseng in F344/N Rats and B6C3F1 Mice
(Gavage Studies)

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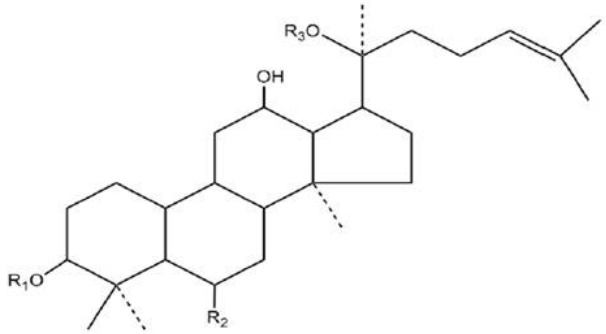
NTP Initiative on Herbal Products and Dietary Supplements[a]

- Approximately one third of the US population is believed to use some form of complementary and alternative medicinal agents that are claimed to prevent and or treat diseases
- The use of herbal medicines and other dietary supplements has increased substantially since passage of the 1994 Dietary Supplement Health and Education Act
- Herbal formulations are not subjected to FDA pre-market approval to ensure their safety or efficacy
- Many of the reports on herbal products are from non-peer-reviewed literature and lack appropriate controlled scientific evaluation
- NTP has many products that have been nominated and selected under this initiative for evaluation of their potential adverse effects in laboratory animals

[a]Chhabra, R.S., Bucher, J.R., Wolfe, M., and Portier, C (2003) Toxicity Characterization of Environmental Chemicals by the US National Toxicology Program: an overview, Int. J. Hyg. Environ. Health 206, 437-445

Background Information on Ginseng

- Fourth most widely used herb in USA
- Used in herbal remedies, dietary supplements, cosmetics, and as food additives, to enhance physical and mental stamina and endurance
- The present studies used *Panax ginseng*, the most popular product on the market
- More than 40 active compounds are identified in ginseng root and categorized into 3 groups: protopenaxadiol ginsenosides, protopenaxatriol ginsenosides, oleanolic acid-saponins
- Composition of ginseng preparations vary. G115 or Ginsana™ is the only product standardized to contain 4% ginsenosides, but proportions of different ginsenosides not guaranteed.



Ginsenoside	R1	R2	R3
20(S)-protopanaxadiols			
Rb1	glucose-glucose	Hydrogen	glucose-glucose
Rb2	glucose-glucose	Hydrogen	glucose-arabinose (pyranose form)
Rc	glucose-glucose	Hydrogen	glucose-arabanose (furanose form)
Rd	glucose-glucose	Hydrogen	glucose
20(S)-protopanaxatriols			
Re	Hydrogen	-O-glucose-rhamnose	Glucose
Rf	Hydrogen	-O-glucose-glucose	Hydrogen
Rg1	Hydrogen	-O-glucose	Glucose
Rg2	Hydrogen	-O-glucose-rhamnose	Hydrogen
Rh1	Hydrogen	-O-glucose	Hydrogen

FIGURE 1
Structures of Common Ginsenosides
Gillis (1997) and Sticher (1998)

Limited Toxicity Information on Ginseng

- A13 week dosed feed study in rats showed no toxic effects at 15 mg/kg of G115 administration
- Chronic exposure for 52 weeks in mice had no effects on body weights and survival at 8 mg/kg of ginseng extract in drinking water, but behavioral response to stress was exaggerated
- In humans ginseng abuse at high doses causes hypertension, nervousness, insomnia, diarrhea and estrogenic toxicity with symptoms such as mammary nodularity and vaginal bleeding
- Some ginsenosides have shown anti-mutagenic activity in a number of experiments

Nomination Rationale

Ginseng was selected for toxicity/carcinogenicity studies because of:

- Significant human exposure
- Lack of adequate toxicity information in the literature

NTP Studies

- 2-Week, 3-month and 2-year toxicity and carcinogenicity studies of ginseng were conducted in male and female F344/N rats and B6C3F1 mice by gavage administration

- Mutagenicity assays were carried out in various *Salmonella* strains and micronuclei frequencies were determined in blood samples collected from 90-day studies in male and female mice

Results of 2-Week Toxicity Studies in Rats and Mice

Dose levels used: 0, 125, 250, 500, 1,000, or 2,000 mg/kg in methyl cellulose

- Survival was not affected
- Body weights of male rats at 2,000 mg/kg were15% lower
- No histopathology attributable to ginseng
- Due to lack of toxicity, selected dose levels for 3-month study were 0, 1,000, 2,000, 3,000, 4,000, 5,000 mg/kg in sterile water

Results of 3-Month Toxicity Studies in Rats and Mice

- Survival not affected
- Body weights comparable to that of controls
- No changes in hematology, clinical chemistry, organ weights, histopathology, sperm parameters, or estrous cycle attributable to ginseng administration
- Due to lack of toxicity, selected dose levels for 2-year studies were 0, 1,250, 2,500, 5,000 mg/kg in sterile water

Results of 2-Year Toxicity and Carcinogenicity Studies

Rats

- Survival of 5,000 mg/kg females lower than other groups (36/50, 27/50/, 34/50, 24/50). Cause of lower survival was not related to ginseng administration
- Final body weights of high dose females were 10% lower than controls
- Incidences of mammary gland fibroadenoma occurred with a negative trend (32/50, 30/50, 30/50,16/50); the decreases were significant in the 5000 mg/kg dose group

Mice

- Generally, survival similar to controls
- Body weights were comparable to controls
- Histopathologic changes were considered not to be related to ginseng treatment

Genetic Toxicology

- Ginseng was not mutagenic in Salmonella strains TA97, TA98, TA100, TA102, TA104, TA1535 with or without S9

- No increases in frequency of micronuclei in peripheral erythrocytes of male and female B6C3F1 mice exposed to ginseng for 3 months

Conclusions

Under the conditions of the 2-year gavage studies, *there was no evidence of carcinogenic activity of ginseng* in F344/N rats or B6C3F1 mice at 1,250, 2,500, or 5,000 mg/kg.

The incidence of mammary gland fibroadenoma was significantly decreased in 5,000 mg/kg female rats.